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Bones, stones, moans & groans – Hypercalcaemia revisited

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## ABSTRACT

Disorders of calcium homeostasis are uncommon but important because of the broad spectrum of potential underlying causes that lie on a spectrum from the benign to the life-threatening. Paediatricians may find them challenging because they do not arise often enough for the investigative approach to be second nature. We report a 4 year old with acute onset profound hypercalcaemia. We focus on an approach to the clinical problem that is based on the potential organ systems affected, namely the gut, bone and kidney. Key biochemical parameters that may help the paediatric team to reach a diagnosis are discussed as well as important components of acute management.

## INTRODUCTION

David, a 4 ½ year old boy, was transferred to the regional children's hospital with a four day history of fever, lethargy, and vomiting. He was constipated, passing urine frequently and complained of sore eyes. He had no past medical or family history of note, and was developmentally normal. His only hospital admission had been for a left ankle fracture two years previously. On examination he was unwell, lethargic, and pale with conjunctival redness. He was mildly dehydrated with dry mucosal membranes and an elevated heart rate (128/min). There were no dysmorphic features, no organomegaly and no obvious skeletal malformation or tenderness.

Initial investigations revealed profound hypercalcaemia – total calcium of 5.07mmol/l and an ionised calcium of 2.76mmol/l. He was hypokalaemic (2.8mmol/l), with borderline hypernatraemia (145mmol/l) and had an elevated creatinine at 68µmol/l (normal range up to 37µmol/l). Phosphate was 1.93mmol/l (0.9-1.8mmol/l), alkaline phosphatase was 185 U/l (150-375U/l). Magnesium and thyroid function were normal. Calcium concentrations were repeated but were again markedly elevated. Full blood count showed normal haemoglobin and platelets, but elevated white count ( $22.1 \times 10^9/l$  of which  $19.07 \times 10^9/l$  were neutrophils). A blood film was unremarkable. Urinalysis demonstrated no glycosuria, but an elevated calcium:creatinine ratio of 6.13mol/mol (normally less than 0.7mmol/mmol)[1].

### COMMENT – Acute hypercalcaemia: Symptoms

The well-known adage of 'bones, stones, moans, and groans' is still relevant in paediatric practice. Symptoms of hypercalcaemia often include abdominal and bone pain, with nausea and vomiting. The associated polyuria can lead to significant dehydration and shock. Persistent chronic hypercalcaemia leads to signs such as conjunctivitis in addition to nephrocalcinosis, renal calculi, renal impairment and peripheral vascular calcification which can have major implications for cardiovascular health later in life. Psychiatric illness can be a feature of paediatric hypercalcaemia but the incidence is poorly defined.

### Acute hypercalcaemia: Initial investigations

Hypercalcaemia is uncommon in the young child, profound hypercalcaemia like this even more so. It was important to confirm that calcium concentrations were abnormal whilst instigating investigations that might help the diagnostic process. Where there is such a significant abnormality in serum electrolytes, emergency management is the main priority. In hypercalcaemic patients it is important to consider the age of the patient and the principle factors that regulate calcium concentrations, notably parathyroid hormone (PTH) and vitamin D (Table 1). Vitamin D metabolism is intrinsically linked to that of calcium. Dietary vitamin D is hydroxylated to 25 hydroxyvitamin D – 25(OH)D, then further hydroxylated by the kidney to 1,25 dihydroxyvitamin D – 1,25(OH)D (by the enzyme 1-alpha hydroxylase) – or inactivated by the liver to 24,25 (OH)D. With modern analysers a PTH value may be obtained outside normal working hours. This is helpful because the presence of low, normal or high PTH values will point the clinician in very different directions when considering the underlying differential diagnosis and pertinent investigations. Saving serum that may be used at a later date is useful in a situation like this.

**Table 1**

## Key hormonal regulators of serum calcium and their actions

Regulator	Actions
PTH	Increases <b>bone</b> reabsorption by osteoclasts*  Increases <b>renal</b> absorption of filtered calcium  Stimulates conversion of 25(OH)D to 1,25(OH)D (activated vitamin D, also called calcitriol)
1,25(OH)D	Increases <b>bone</b> reabsorption by osteoclasts  Increases <b>renal</b> tubular reabsorption of filtered calcium  Increases <b>intestinal</b> absorption of calcium via active transport
Calcitonin (thought to be of little physiological significance beyond the neonatal period)	Inhibits <b>bone</b> reabsorption by osteoclasts  Reduces <b>renal</b> absorption of filtered calcium  Decreases <b>intestinal</b> absorption of calcium

\* - the mechanisms of PTH on bone metabolism are complex; here we provide a simplified overview.

### Acute hypercalcaemia: Management

The acute management of hypercalcaemia centres on enhancing physiological calcium excretion where possible.

#### 1- Intravenous fluids

Under normal circumstances, filtered calcium is predominantly passively reabsorbed together with sodium in the proximal tubule (Fig 1A) although a fraction (10-15%) of calcium is later actively reabsorbed within the distal convoluted tubule. Sodium is also reabsorbed via the Na-K-2Cl channel and potassium is later returned to the urine via the renal outer medullary potassium (ROMK) channel to maintain the diffusion gradient.

Hypercalcaemia impacts on sodium (and thus water) reabsorption leading to a diuresis. This may be caused by either the greater ionic charge of calcium compromising the NaK2CL channel or an inherent increased osmotic effect of calcium within the urine. The higher positive charge of calcium also inhibits potassium transfer via ROMK back into the urine in the proximal tubule. To maintain normovolaemia, sodium is then preferentially reabsorbed later in the tubule in exchange for potassium leading to hypokalaemia.

Volume expansion enhances renal calcium excretion. Expanding intravascular volume with saline reduces initial sodium reabsorption, so less calcium is passively reabsorbed and less potassium is lost through distal exchange (Fig 1B). Hyperhydration with 3l/m<sup>2</sup>/24 hours of

0.9% saline can significantly improve calcium excretion and is particularly useful if the child is already volume depleted.

## 2- Loop diuretics

If the child is well-hydrated calcium excretion can be further increased via the administration of a loop diuretic, such as furosemide. Loop diuretics block the Na-K-2Cl co-transporter in the thick ascending limb of the loop of Henle. Blocking sodium reabsorption again reduces the concurrent calcium reabsorption that occurs passively, but will exacerbate hypokalaemia. This effectively mimics the normal physiological response to high serum calcium, which is why diuretics should be used with care, as intravascular depletion will lead to exacerbation of the hypercalcaemia.

## 3- Dialysis

In cases where severe hypercalcaemia is associated with oliguric renal impairment, acute haemodialysis may be needed to rapidly remove calcium.

**David received intravenous fluids but total calcium levels rose to 5.55mmol/l. The renal impairment resolved, but his hypokalaemia worsened ( $K^+$  of 2.1mmol/l). Whilst David was being treated and whilst PTH and Vitamin D levels were awaited, the differential diagnosis was considered in greater detail.**

**David had been staying with his grandparents in a caravan in the days leading up to his presentation. One of the grandparents was on a flavoured combined vitamin D/calcium preparation, but the family did not feel that accidental ingestion was likely.**

## COMMENT – Causes of hypercalcaemia

Hypercalcaemia can be categorised in a number of ways, for example– by age (infancy or beyond), or according to the presence of normal/elevated or low PTH levels. The latter approach has recently been reviewed in this journal, with a thorough discussion of the pathophysiological mechanisms behind various causes of hypercalcaemia[2]. Here, we have opted to focus on mechanism and whether elevated blood calcium concentrations can be primarily linked to pathology in the gut, bone or kidney. Specifically, altered calcium concentrations may reflect dietary absorption in the gastro-intestinal tract (**GUT**), altered storage/release from the skeleton (**BONE**), or altered renal handling (**KIDNEY**) – Table 2. In many instances the hypercalcaemia will reflect alterations in more than one of these organ systems although here we will consider each mechanism separately for the sake of clarity.

**Table 2**

Causes of hypercalcaemia by mechanism

<b>Excess vitamin D intake or generation with increased gut absorption</b>	<b>Abnormal bone turnover</b>	<b>Impaired renal clearance</b>
Excess exogenous Vit D	Malignancy	Familial      hypocalciuric

		hypercalcaemia (FHH)
Idiopathic hypercalcaemia of infancy /CYP24A1 mutation	Hypophosphatasia	Chronic renal impairment
Hyperparathyroidism	Hyperparathyroidism	Hyperparathyroidism
Williams syndrome		Bartters' syndrome
Subcutaneous fat necrosis		
Granulomatous disease		

### Differential diagnosis of hypercalcaemia – GUT absorption

Accidental ingestion is a key consideration in a clinical picture like this and it was important to establish whether there was any possibility of David consuming excessive quantities of calcium or vitamin D which will enhance calcium absorption from the gut. These preparations are likely to be more widespread in homes and drug cabinets today than they were in the past. The deliberate flavouring of many of these medicines to make them more palatable may increase the risk of accidental overdosage.

Preparations of vitamin D may be 'inactive' i.e. requiring hydroxylation by the liver (25-hydroxylation) and the kidney (1-hydroxylation), or they may be 'active' preparations already, such as calcitriol (1,25(OH)D). Excessive ingestion of inactive vitamin D preparations such as ergocalciferol may not cause any clinical sequelae[3]. There are likely to be inter-individual differences in susceptibility to hypercalcaemia.

The minimal dose of Vitamin D that may cause harm remains contentious, though is probably at least 10,000 units daily[4]. There is inter-individual variability in sensitivity to exogenous vitamin D which reflect differences in vitamin D metabolism and tissue sensitivity. This was highlighted by the development of infant hypercalcaemia following vitamin D supplementation of formula milk in the UK in some individuals but not everyone. This may in part reflect CYP24A1 gene activity (the gene that encodes the enzyme involved in 1,25(OH)D degradation) with affected children being less able to regulate their level of activated vitamin D[5]. The pharmacokinetics of vitamin D, with rising concentrations up to a month post-ingestion is a further key consideration[6].

Vitamin D levels may also be raised due to excessive endogenous vitamin D generation – this will be discussed later.

**Total vitamin D and PTH concentrations were available within 24 hours. The PTH level was low (0.6pmol/l, normal 1.1-6.4pmol/l) and the vitamin D level was 52nmol/l (normal >50 nmol/l, 25-50 nmol/l 'insufficient', <25 nmol/l 'deficient') and hence not suggestive of vitamin D toxicity. The 1,25(OH)D level was low-normal at 30pmol/l (normal 20-120 pmol/l) in keeping with a low PTH.**

**Given the patients' age and the severity of his hypercalcaemia, malignancy was considered to be the most likely underlying cause although there were no specific**

pointers towards a malignant focus. A blood film was normal as were plain films of his chest and abdomen. Further imaging and a bone marrow biopsy to exclude malignancy required a general anaesthetic. More focused treatment was therefore instituted as a matter of relative urgency to try and reduce calcium levels pre-anaesthesia.

### ***COMMENT – Ongoing management of hypercalcaemia***

Less acute management of hypercalcaemia will focus on treating the underlying cause. Management and investigation typically run together. Sometimes, as in this case, more definitive treatment may be required to permit further investigation.

#### **1- Calcitonin**

Calcitonin is an endogenous polypeptide that directly opposes many of the effects of PTH, though its true physiological role in humans is unclear. Calcitonin mainly inhibits osteoclastic activity, but also inhibits intestinal and renal tubule calcium reabsorption. Therapeutically administered calcitonin is derived from the polypeptide found in salmon, salmon calcitonin, which is more biologically active[7]. Calcitonin is almost exclusively metabolised by the kidneys, so may accumulate in renal impairment, though this does not seem to be a mechanism that contributes to hypercalcaemia in renal disease. Administration is by intravenous infusion, by subcutaneous/intramuscular injection or intranasally (the latter for more chronic use). Adverse effects of calcitonin administration include nausea, flushing, paraesthesia, and local inflammation at the site of administration. These adverse effects are common, affecting approximately 20% of patients.

#### **2- Bisphosphonates**

Bisphosphonates, such as pamidronate, bind to calcium. Approximately 50% of the drug is then excreted by the kidney and the remainder is absorbed into bone. Normal bone homeostasis is disrupted as bisphosphonates trigger apoptosis of osteoclasts. [8]. Bisphosphonates will reduce calcium levels within 24 hours and their enduring effect means that some patients may then become hypocalcaemic which in turn may require treatment. Bisphosphonates should be used with caution in renal impairment and re-hydration is essential prior to commencing therapy. Reports of renal damage are attributed to rapid infusion of older bisphosphonate agents. Adverse effects include an acute phase reaction on first administration with pyrexia, myalgia, elevation of inflammatory markers, and lymphopenia. Gastro-intestinal upset and bone pain may also occur although paediatric patients appear less susceptible to adverse effects than adults. Hypocalcaemia post-administration can be particularly troublesome in patients who have a suboptimal vitamin D status.

#### **3- Oral steroids e.g. prednisolone**

The mechanism whereby glucocorticoids reduce calcium concentrations is complex but a key action is the suppression of 25(OH)D activation to 1,25(OH)D. Steroids are frequently used in the management of malignancy because of their toxic effect on leukaemia cells. It is therefore imperative that malignancy has been excluded before steroid is administered as a treatment for hypercalcaemia. Bone marrow aspiration may be required before steroid is administered.



Steroids also have a role in other conditions where there is excessive activation of vitamin D, such as granulomatous diseases or subcutaneous fat necrosis. Again, the mechanism is via reduction in 1,25(OH)D generation.

#### 4 – Ketoconazole

Ketoconazole inhibits multiple enzymes, including the enzyme 1-alpha hydroxylase. It has therefore been used for the treatment of infantile idiopathic hypercalcaemia[9], hyperparathyroidism, sarcoidosis, and other granulomatous causes of hypercalcaemia. The adverse effects of ketoconazole include transaminitis, renal impairment, with hepatic impairment or failure in rarer cases. This side-effect profile limits its' value in the management of hypercalcaemia.

**One of the above management strategies will frequently be successful in reducing serum calcium to an acceptable level. In Davids' case the step-wise administration of fluid, calcitonin, then oral prednisolone, and finally a single dose of pamidronate (1mg/kg) was successful in restoring serum calcium to normal. A step-wise approach is usually appropriate when treating hypercalcaemia although the interval between treatments was relatively short in David's case because of the severity of the hypercalcaemia. The reduction in serum calcium was associated with a marked improvement in his clinical condition.**

#### **COMMENT: Differential diagnosis of hypercalcaemia – Altered BONE turnover**

Hypercalcaemia may reflect abnormal bone formation or abnormal bone breakdown. Abnormal bone turnover is a feature of immobility, abnormal muscle function and hypophosphatasia. The patient was not immobile and hypophosphatasia was excluded on the basis of patient age and a normal alkaline phosphatase at presentation. It was imperative to rule out the most significant cause of abnormal calcium release from bone in the presence of a low PTH – malignancy.

Hypercalcaemia is reported to complicate less than 1% of paediatric malignancies[10], but is far commoner in adult malignancy[11]. Mechanisms include:

- Destruction of the bony skeleton by an actively osteolytic lesion.
- Humoral factors produced by malignant cells promoting bone resorption - TNF- $\alpha$ , IL-1, IL-6, and 1,25(OH)D
- Excess PTHrP - The commonest factor associated with hypercalcaemia is parathyroid hormone-related peptide (PTHrP)[12]. PTHrP has equivalent biological activity to PTH and increases serum calcium through its effects on bone [promoting release], the kidney [reduced filtration], and indirectly on the gut [via an increase in activated vitamin D which increases calcium absorption]. Production of PTHrP in this setting is dysregulated and hypercalcaemia results.

A bone marrow trephine did not demonstrate any evidence of malignancy and David was subsequently found to have normal PTHrP concentrations (<1pmol/l, normal <1.8pmol/l). A wrist radiograph was normal. David underwent a whole body Technetium<sup>99</sup> scan, alongside single positron emission computed tomography (SPECT) of his chest and abdomen. Isotope uptake by the skeleton was normal apart from a mild diffusely increased uptake in his left ankle, but a marked increase in uptake over what would typically be expected in his stomach, lungs, and kidneys, attributed to his hypercalcaemia (Figure 2). A plain film of the left foot demonstrated two minute cortical lucencies in the distal fibular metaphysis, felt to be of no pathological significance.

#### **COMMENT – Imaging**

The extensive imaging that David received was partly motivated by the strong clinical belief that malignancy was the most likely cause of his hypercalcaemia.

The increased uptake on the Technetium scan in the stomach, lungs, and kidneys, is felt to represent transient calcium deposition within those tissues, as a result of the significant hypercalcaemia. This then leads to a 'positive' finding as extra-osseous uptake occurs[13].

David subsequently developed hypocalcaemia (a well-recognised consequence of bisphosphonate therapy) three days after the pamidronate, and required oral calcium supplementation and optimisation of his vitamin D status. Importantly, in the presence of hypocalcaemia, his urinary calcium excretion diminished to undetectable levels, confirming that renal filtration of calcium was normal. Abdominal ultrasonography demonstrated bilaterally large (>75<sup>th</sup> centile) echogenic kidneys with reduced (though preserved) corticomedullary differentiation. No nephrocalcinosis was seen. There was splenomegaly (8.2cm splenic length) but normal liver, gallbladder, and pancreas.

#### **COMMENT: Differential diagnosis of hypercalcaemia – KIDNEY excretion**

An important observation was that PTH concentrations were abnormally low though not totally suppressed. Normal PTH levels in the context of hypercalcaemia should make one consider calcium sensing receptor (CaSR) and related defects which can result in an altered calcium 'set-point'[14,]. Calcium sensing receptors are present on the parathyroid gland, but also the kidney, which regulates calcium excretion (as discussed earlier). If the kidney cannot detect urinary calcium, there is inappropriate reabsorption, leading to hypercalcaemia. Disorders of the CaSR may present with severe hypercalcaemia in the neonatal period (Neonatal severe hyperparathyroidism, typically associated with 2 abnormal CaSR alleles) or with asymptomatic hypercalcaemia in childhood (typically associated with one abnormal CaSR allele)[15]. The latter abnormality is called familial hypocalciuric hypercalcaemia (FHH) and asymptomatic hypercalcaemia will frequently be found in one of the parents. It is relatively unusual for the hypercalcaemia of FHH to be severe, and the vast majority of cases are asymptomatic. The elevated urinary calcium:creatinine ratio at presentation also argues against a CaSR defect in David's case.

Excessive PTH or Vitamin D may lead to over-resorption of bone and greater serum calcium levels than can readily be excreted by the kidney. In these situations, urinary calcium excretion is appropriately high in an attempt to normalise serum calcium. Chronic hypercalcaemia will often lead to nephrocalcinosis, as the hypercalcuria predisposes to calculus formation. In contrast, acute hypercalcaemia may not give sufficient time for precipitation. The absence of nephrocalcinosis on ultrasound in David's case was an important observation because it indicated that the development of hypercalcaemia was an acute process.

**Investigations had thus excluded excessive GUT absorption and malignancy resulting in calcium release from BONE and had indicated apparently normal KIDNEY excretion. The other cause of excessive GUT absorption is endogenous generation of active vitamin D metabolites which may result from infection and in particular granulomatous disease. During the course of his admission David had a raised C-reactive protein, initially 31mg/l, which increased to 71 mg/l and then normalised. He had no obvious infective contacts for tuberculosis, no history of recent foreign travel and no regular contact with cats. Serum angiotensin-converting enzyme (ACE) was initially elevated (80U/l, normal 8-52U/l) but subsequently normalised (51U/l). Rheumatoid Factor was very mildly elevated (21IU/ml, normal 0-19IU/ml) but all other immunological investigations including complement studies, EBV and CMV serology, and Quantiferon-GOLD were normal.**

#### **COMMENT: Differential diagnosis of hypercalcaemia – Granulomatous disease**

Granuloma are caused by persistence of macrophage activation either through an inability to clear the initial source (e.g. intracellular bacteria, foreign material or inefficient microbial killing in chronic granulomatous disease), or an abnormality in the processes that 'switch off' the macrophage.

This on-going activation of T-cells and macrophages within the granuloma leads to endogenous expression of 1,25 $\alpha$ -hydroxylase and excessive endogenous activated vitamin D (1,25(OH)D)[16]. This has exactly the same effect on GUT as excessive exogenous vitamin D, as discussed earlier.

Other mycobacteria may also lead to granuloma formation. *Bartonella henselae*, the causative organism for cat scratch fever, is typically associated with a history of superficial injury from a newly acquired kitten, with granuloma formation localised to the draining lymph nodes of the injury. Other conditions commonly predisposing to granuloma include cryptococcosis, leprosy, and histoplasmosis.

Another important, though rare, differential in the paediatric population is sarcoidosis[17]. Granulomata form in response to an unknown trigger (still a focus of research). Paediatric presentation tends to be delayed, due to its rarity, and has obvious lifelong implications. The presence of hilar lymphadenopathy would be characteristic, as is elevation of serum ACE. Rheumatoid arthritis may also present with granulomata.

**None of the features in David's history and examination were suggestive of an infective cause, nor did any of his extensive imaging demonstrate any visible**

granuloma. The borderline rheumatoid factor, and initial elevation of serum ACE might suggest an abnormality of macrophage function, but the normalisation of all parameters suggested that this was not the case.

In the absence of a specific cause David underwent an MRI of his head, spine, chest, abdomen, and pelvis, looking for evidence of unrecognised foci of granulomatous disease or malignancy but no abnormality was identified.

By this point recognised causes of acute hypercalcaemia in childhood had been excluded, and we considered whether he had an atypical presentation of a neonatal disorder.

#### COMMENT: Infantile Hypercalcaemia

The differential diagnosis of neonatal hypercalcaemia is broad (Table 3) and in David's case many of the neonatal diagnoses, such as hypophosphatasia, could be excluded on the basis of history or age alone. The hypercalcaemia associated with Williams syndrome may occasionally persist into early childhood but David did not have the associated clinical features.

More recently, mutations within CYP24A1 (24-hydroxylase) which inactivates vitamin D have been identified as a cause of infant hypercalcaemia[5]. Though most affected patients develop hypercalcaemia and become symptomatic in infancy, mutational analysis of families has identified apparently asymptomatic older siblings. Screening for CYP24A1 mutations is slowly entering the investigative protocol for hypercalcaemia. The acute onset of David's hypercalcaemia argues against this diagnosis, as do the normal 1,25(OH)D levels and the fact that his hypercalcaemia resolved and has not recurred.

**Table 3**

Important causes of hypercalcaemia according to age

PTH	Infancy	Childhood
Normal or raised	<ul style="list-style-type: none"> <li>Neonatal severe hyperparathyroidism (calcium-sensing receptor defect)</li> </ul>	<ul style="list-style-type: none"> <li>Calcium sensing receptor defect (FHH)</li> <li>Hyperparathyroidism</li> </ul>
Low	<ul style="list-style-type: none"> <li>Williams syndrome</li> <li>Vitamin D excess</li> <li>Hypophosphatasia</li> <li>Mutations within the gene coding for this enzyme, CYP24A1</li> <li>Idiopathic hypercalcaemia of infancy</li> </ul>	<ul style="list-style-type: none"> <li>Malignancy e.g. lymphoma, leukaemia</li> <li>Vitamin D excess</li> <li>Granulomatous disease</li> <li>Thyrotoxicosis</li> </ul>

David's calcium rose to low normal levels with supplementation and his PTH normalised. Having effectively excluded malignancy and granulomatous diseases we opted to monitor his progress in the out-patient setting. Vitamin D levels fell to 21nmol/l four days post-admission, then increased to normal values (71nmol/l) following supplementation.

No acute cause was identified and there has been no recurrence of either symptoms or hypercalcaemia. A repeat renal ultrasound demonstrated bilateral normal-sized kidneys. David was reviewed one month post-presentation at which point calcium levels were normal. He re-presented eight weeks later with conjunctivitis and lymphadenopathy but calcium levels were normal and this was felt to be intercurrent infection and quickly settled. David remains well with normal serum calcium six months following presentation and has been discharged from our service but with ongoing follow-up with his local paediatrician. It is interesting to reflect on the fact that an underlying diagnosis may not be found in up to 15% of adults with hypercalcaemia[18] .

#### **COMMENT: Summary**

Hypercalcaemia may reflect excessive gut absorption, abnormal bone turnover or altered renal handling. The presentation of acute, profound hypercalcaemia in a previously well child should raise the possibility of an underlying malignancy. Measuring PTH concentrations, Vitamin D (25(OH)D) and, in selected cases, 1,25(OH)D, is of great importance when attempting to arrive at a diagnosis. This case highlights the fact that a definitive explanation for a clinical problem is not always identified and managing uncertainty remains a regular component of paediatric practice.

## MCQs

### 1) Renal excretion of calcium:

- A) Is regulated by CaSR on the parathyroid
- B) Is independent of sodium handling
- C) Is elevated in FHH
- D) Is associated with nephrocalcinosis in acute hypercalcaemia
- E) May be increased through the administration of IV fluids

### 2) Key considerations in hypercalcaemia management are as follows:

- A) Loop diuretics should be considered at an early stage.
- B) It is vital to correct hypercalcaemia before investigations are performed
- C) Oral glucocorticoids are a useful first line treatment in haematological malignancies
- D) Bisphosphonates may cause hypocalcaemia
- E) Avoid hyperhydration if creatinine levels are raised

### 3) Granulomatous disease

- A) Occurs when macrophages cannot be activated
- B) Causes hypercalcaemia through an effect on vitamin D metabolism
- C) Is exclusively infectious in paediatric populations
- D) Is associated with an elevated PTH concentration
- E) Is characterised by a low serum ACE

### 4) Hypercalcaemia

- A) Caused by inherited conditions invariably presents within the 1<sup>st</sup> year of life
- B) May cause a compensatory hyperkalaemia
- C) Will normally trigger a rise in alkaline phosphatase
- D) May result from ingestion of vitamin D tablets
- E) Always requires treatment

### 5) Mechanisms resulting in the hypercalcaemia of malignancy include:

- A) Reduced activity of CYP24A1
- B) Over-production of PTH by bone marrow stem cells

- C) Excessive breakdown of bone by osteoclast activation
- D) Impaired calcitonin production
- E) Cytokine production by bony metastases

**Correct answers**

**1 E**

**2 D**

**3 B**

**4 D**

**5 C E**

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**Competing Interests**

There are no competing interests to declare

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